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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,442	04/16/2001	Donald S. Karanewsky	480140.444D1	6279

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,442	KARANEWSKY ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-36,39 and 41-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,38 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group II is acknowledged, as are the elected species ((a) the compound of example 79, and (b) chronic active hepatitis as the disease to be treated).

Claims 1-36, 39, 41-45 are withdrawn from consideration

*

35 U.S.C §101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 40 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 40 recites the term "preventing". Even if one were to stipulate that the claimed compounds can be used to treat the recited diseases, it would still not follow therefrom that actual prevention can be achieved. Prevention means that out of a given population of test subjects, not a single one develops a disease. The bar that

must be overcome to demonstrate prevention is quite high, and not even an initial step towards demonstrating this has been undertaken. This particular ground of rejection can be overcome by deleting the term "preventing".

Claim 40 is rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 40 is also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown (table 3, page 63) that the claimed compounds can inhibit one or more caspases. Based on this, applicants are asserting the the claimed compounds can be used to treat any of several diseases including the following: meningitis, salpingitis,

septic shock, respiratory diseases, inflammatory conditions, arthritis, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, reperfusion injury; ischemic diseases such as myocardial infarction, stroke and ischemic kidney disease; hypersensitivity; autoimmune diseases, multiple sclerosis, osteoporosis, Paget's Disease, neurodegenerative disease, Alzheimer's disease, and Parkinson's disease. It is also asserted that the claimed compounds will be effective to repopulate hematopoietic cells following chemo- and radiation therapy and for prolonging organ viability for use in transplantation.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor

antagonist was not active as an anti-inflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" after stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

With respect to claim 40, Read S. J. (*Drugs and Aging* **14** (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfill their promise in clinical trials.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of human disease leads to "unpredictable" results; undue experimentation would be required to practice the claimed invention. It is suggested that each of the method-of-use claims be cancelled, and that the term "pharmaceutical" not be recited in any claim subsequently added.

Notwithstanding the foregoing, the possibility exists that the following claim might be enabled .

> *A method of inhibiting apoptosis comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to inhibit a caspase.*

If such a claim is added, however, it is suggested that applicants provide at least one reference which shows that, at the time of the invention, it was known that caspase inhibitors are effective to inhibit apoptosis.

In addition, if deemed appropriate, a claims drawn to a method of inhibiting a caspase can be added.

✧

Claims 37, 38 and 40 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the elected claims is dependent on a non-elected claim.

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37-38 are rejected under 35 U.S.C. §102(b) as being anticipated by Dolle (USP 5,585,357).

Dolle discloses (col 19, line 27+) the compound of example 64. This compound is encompassed by instant claim 1 when the substituent variables correspond as follows:

R^1 = naphthyl
X = $-CH_2-$
n = 0
A = valine
R^2 = hydrogen
R^3 = hydrogen
B = $-CH_2-Z-R^{16}$
Z = -O-
R^{16} = heteroaryl

Also disclosed (col 7, line 61) is that various inflammatory and autoimmune diseases can be treated. Thus, the claims are anticipated.

✧

The following is a quotation of 35 USC. 103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under

subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 40 is rejected under 35 U.S.C. 103 as being unpatentable over Dolle (USP 5,585,357).

Some of the teachings of Dolle are indicated above. Dolle also teaches that the compounds inhibit IL-1 production, and that they can be used to treat IL-1 mediated diseases. Dolle does not list ischemia among the diseases which can be treated. However, the cardiovascular specialist of ordinary skill is aware that IL-1 is involved in the onset of ischemia. Accordingly, the artisan of ordinary skill would reason that since IL-1 is involved in ischemia, inhibition of IL-1 production will result in a successful therapy.

Thus, the claim is rendered obvious.

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600